UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,317	07/06/2006	Birgit Bollbuck	PA/4-33165A	2729

75074 7590 12/24/2008

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
400 TECHNOLOGY SQUARE
CAMBRIDGE, MA 02139

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
12/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,317	BOLLBUCK ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,8,9 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,8,9 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070109*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 5-6, 8-9 and 12-14 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-3, 6, 8-9 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula I or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for an ester or prodrug thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims recite "A compound ... or a pharmaceutically acceptable salt, **ester** or

prodrug thereof" wherein there is insufficient description in the specification regarding the types of **esters** or **prodrugs** intended by the recitation. The term 'prodrug' generally represents any type of ester, amide, active metabolite, residue, etc. of a compound, which is transformed to an active agent *in vivo*. The specification at page 8 provides that – 'prodrug ester derivatives are those convertible by solvolysis or cleavage under physiological conditions to the corresponding agents of the invention which comprise free hydroxyl groups'. In the instant case, the specification does not provide what 'types of esters or prodrugs' of the compounds of formula I are intended. The structural formula in the claim is a specific structural representation having specific defined substituent groups. There is no disclosure regarding any acid/ester or other derivatives of the compounds of formula I disclosed in the specification. A 'prodrug' is any compound which is pharmaceutically active *in vivo* when it undergoes transformation and the specification does not provide any disclosure of what these compounds might be that *in vivo* transform in to the instantly claimed compounds.

a) Finding a prodrug or ester is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Thus,

determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrug esters is found in the page 8.

c) There is no working example of a prodrug ester of a compound the formula I.

d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body.

e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. A prodrug as defined by Bundgaard (Design of Prodrugs) "is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug" (see page 1). Thus, an important requirement of prodrugs is that they be pharmacologically inactive. The scope of the term '*in vivo* hydrolysable ester' is quite broad.

f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience.

g) It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug". Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

Since the structural formulae already include acid as well as ester functional groups (see for example, the definition of R1 which includes the term –C(O)-Rx wherein Rx is OH, loweralkoxy), deletion of the terms "ester or prodrug" will obviate the rejection.

2. Claims 6, 8, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating rheumatoid arthritis, does not reasonably provide enablement for a method of inhibiting IKK activity in a patient suffering from an IKK mediate disease; a pharmaceutical composition for the prevention or the treatment of an autoimmune disease or inflammatory disease or condition; a method of inhibiting production of TNF, TNFα, IL-1 or COX-2; or a method for the treatment of conditions mediated by TNF, TNFα, IL-1 or COX-2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The

nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims recite 'a method of inhibiting IKK activity in a patient suffering from an IKK mediate disease; a pharmaceutical composition for the prevention or the treatment of an autoimmune disease or inflammatory disease or condition; a method of inhibiting production of TNF, TNFα, IL-1 or COX-2; or a method for the treatment of conditions mediated by TNF, TNFα, IL-1 or COX-2'. The instant claims appear to be in 'reach-through' format. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification. Further, there is no disclosure regarding how the patient in need of such activity is identified and further, how an inhibition of IKK activity is generally produced in the patient. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art.

First, the instant claims cover 'conditions' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test assay and procedure are provided in Experimental Example 1 of the specification pages 197-201 related to inhibition of TNF-α production and it was concluded that 'agents of the invention are potent inhibitors of

TNF-α release'. There is nothing in the disclosure regarding how this *in vitro* TNF-α inhibitory data of five specific compounds correlates to the treatment of various conditions encompassed by the instant claims using the entire genus as recited in the instant claims. The disorders encompassed by the instant claims include various inflammatory diseases, autoimmune diseases, organ or tissue transplant rejection, etc. which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Enablement for the scope of "inflammatory diseases" or 'inflammation' generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase

inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Claim 8 is directed to 'a composition for the prevention or the treatment of an autoimmune or inflammatory disease or condition' and the specification did not provide any

competent tests or data to establish that the compounds have the claimed activity of the composition. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Furthermore, the scope of the composition claim 8, is not adequately enabled solely based on TNF-α inhibitory activity provided in the specification. The instant claims are drawn to 'a composition for **prevention** ...' of diseases such as inflammatory diseases, autoimmune diseases, etc., and therefore, the instant claim language embraces disorders not only for the treatment, but for "prevention" which is not remotely enabled. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis

and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. Thus, it is inconceivable as to how the claimed compounds can not only treat but also "prevent" a myriad of diseases with different etiologies. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-6, 8-9 and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In the claims, it is not clear what types of 'esters or prodrugs' of the compounds of formula I are intended. The structural formula in the claim is a specific structural representation having specific defined substituent groups which includes both free acid

form as well as the corresponding ester forms, see for example, the definition of R1 which contains the term –C(O)-Rx wherein Rx can be OH or alkoxy.

2. Regarding claim 2, the phrase "e.g." (or "for example") renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

3. In claim 2, the recitation "heteroaryl, **conveniently** containing … **including** fused ring heteroaryl, **e.g.** optionally substituted …" contains several terms: "conveniently"; "including"; "e.g." - that are improper language and are indefinite. These terms render the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "including"; "e.g.") thereby rendering the scope of the claim unascertainable.

4. In claim 3, the recitation "aryl **(including** heteroaryl)" (see page 5, line 3) in the definition of R2" appears to be out of place.

> R2" is optionally substituted phenyl, thiophenyl, benzthiophenyl, pyridinyl, naphthalenyl or indolyl aryl (including heteroaryl),

5. First, there is no 'comma' (,) separating the terms "indolyl" and "aryl". Next the term "including" is indefinite because the claim includes elements not actually disclosed (those encompassed by "including") thereby rendering the scope of the claim unascertainable. The claim further contains recitation - "lower alkyl **(including** cycloalkyl)" (all occurrences), which is also indefinite for the same reason stated above.

6. Claim 5 recites "wherein the R substituents are as defined above", however, does not contain the definitions within the claim. An independent claim must contain all

limitations within the claim or should depend from another claim which contains the limitations.

7. In claim 12, which lists numerous species, following one of the compound, the recitation "Example 91" (see page 12, lines 15-16) appears to be out of place.

> 1-{5-[2-(2,2,6,6-Tetramethyl-piperidin-4-ylamino)-pyrimidin-4-yl]-thiophen-2-yl}-ethanone Example 91;

8. The claim also contains the recitation - "Example 161a" (see page 15, lines 28-29); "ple 201" (see page 17, lines 13-14); etc. all of which are redundant.

9. Claim 12, contains the recitation "A solution of toluene-4-sulfonic acid 3-{4- ....ester (80 mg, 0.15 mmol), (Step A of Example 190), KCN (20;" (see page 17, lines 2-3) which appears to be out of place.

> A solution of toluene-4-sulfonic acid 3-{4-[2-(2,2,6,6-tetramethyl-piperidin-4-ylamino)-pyrimidin-4-yl]-phenyl}-propyl ester (80 mg, 0.15 mmol), (Step A of Example 190), KCN (20;

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-6, 8-9 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al., WO 96/40143. The reference teaches substituted imidazole compounds having cytokine inhibitory activity, see formula (I) in page 4 and the compounds of the Examples, particularly the compound of Example 13. The instant claims exclude reference disclosed compounds wherein R^1 is methyl, see the proviso statement in the definition of R2: "wherein aryl is not 4-(4-fluorophenyl)-1(1-methlpiperidin-4-yl)imidazole", however, include compounds wherein R2 is a structural analog of the above fragment, i.e., wherein R2 is 4-(4-fluoropheyl)-1(piperidin-4-yl)imidazole (i.e, piperidin-4-yl in place of 1-methylpiperidin-4-yl or H in place of CH_3). Therefore, the instantly claimed compounds differ from the reference compounds by a having H vs. CH_3 or by a $-CH_2$ group. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural analog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally analogous compounds are expected to possess similar properties. It has been held that compounds that are structurally analogous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results.

Note: Applicant's attention is directed to U.S. Patent Application Publication 2007/0270418 which while is not a competent reference against the instantly claimed invention,

claims subject matter that is substantially similar to that claimed herein, see the claims which include the compound listed in Table 1, e.g., CCLXXXI (page 59). Unless applicants can demonstrate that the instant claims are patentably distinct from the claims in this US patent, the only way to overcome these patents is by way of interference proceedings or removal of the conflicting subject matter. See MPEP § 2306.

Receipt is acknowledged of the Information Disclosure Statement filed on January 9, 2007 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

December 25, 2008